

# **Cardiac Arrest Etiology and Associated Cognitive Impairment in Survivors**

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### **Abstract**

Background: Cardiac arrest is a significant public health problem, impacting over 500,000 people in the United States annually. The four major etiologies of arrest are cardiac, respiratory, traumatic, and other/unknown. The objective was to determine the impact of etiology on cognition in cardiac arrest survivors using the Montreal Cognitive Assessment (MOCA).

Hypothesis: Cardiac arrest etiology impacts cognitive exam score, and patient demographics and characteristics modify that relationship.

Methods: A retrospective cohort analysis was performed on all Pittsburgh Post Cardiac Arrest Service (PCAS) patients between 2012 and 2018. Patient data were acquired from the PCAS database and through medical record review. T-tests, linear regression, logistic regression, and tests of variance were used to assess the relationships between cognitive exam score and modifying factors. MOCA score was analyzed as a continuous percent score and as a binomial indicator of normal cognition. For all statistical tests, an alpha level of 0.05 was used to determine significance.

Results: MOCA score as a continuous measure was not significantly associated with etiology. When MOCA score was converted to a binomial indicator of normal cognition, respiratory, traumatic, and other/unknown etiologies performed significantly worse than cardiac etiology arrest when age, sex, witnessed status, length of ICU stay and coma were controlled for. These findings

were nullified when time from arrest to MOCA administration was introduced to the regression model.

Conclusions: Respiratory, traumatic, and other/unknown etiologies were more likely to exhibit abnormal cognition on the MOCA than those with a cardiac etiology. The etiological findings were nullified when time to cognitive examination was controlled for. Timing appears to be more influential on cognitive performance than cardiac arrest etiology.

Public Health Significance: Survivors struggled with delayed recall regardless of etiology, and respiratory arrests had increased odds of impaired language and attention. This study supports the use of the MOCA serially to assess the impact of timing on cognitive performance after cardiac arrest. Knowledge that timing of exam can impact score more than etiology and that scores improve over time will improve the focus of healthcare and rehabilitation for survivors prior to hospital discharge and in the months of recovery afterward.

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## Preface

I would first like to extend a heartfelt thank you to my committee members for dedicating their time and brainpower to help bring this project to life. Dr. Songer was the first professor I met in the Graduate School of Public Health and has been my academic advisor for the duration. It seems only fitting that he helped see this project (and my academic journey) through to the end. Dr. Rittenberger has been my PI and friend for several years who encouraged me to take a seedling of an idea from when I was a 20-year-old undergrad and turn it into a 50+ page master's thesis that has spawned many new ideas for me to pursue over the coming years. Dr. Rosso was kind enough to come onboard my committee to give her unique perspective and neuroscience expertise, which were very much needed and highly valued. This project would not have succeeded without them.

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scientist, my parents delivered me to their door with a curious mind and the necessary work ethic to produce quality scientific literature. I literally would not be where I am today without them.

This research was brought to you by a copious amount of tacos with a healthy splash of lime juice consumed at or around 1 am.

## **1.0 Introduction – Thesis Project**

Cardiac arrest is a significant public health problem that impacts more than 500,000 people each year in the United States.<sup>1</sup> Medically defined, cardiac arrest is the state of complete cessation of mechanical activity of the heart that is needed to sustain life. In only a few minutes, the lack of oxygenated blood flow causes heart and brain cells to die, and in many cases, the physiological insult is unsurvivable. Survival rates vary by type of arrest and location but are estimated to be as low as 8% in certain populations.<sup>2</sup>

Due to the high fatality rate, much of the body of cardiac arrest-related research is rightfully focused on increasing survivorship. However, those who do survive experience both functional and cognitive impairment, which can detract from quality of life.<sup>3</sup> Published work has neither focused on how the physiological cause of a cardiac arrest is linked to cognitive impairment nor determined the frequency of certain types of cognitive impairment stratified by etiology in this population. The focus of this thesis will be on one specific post-arrest complication: cognitive impairment, including memory loss,<sup>4-8</sup> impaired executive function,<sup>7</sup> and decreased psychomotor function.<sup>7,9</sup> These impairments can last for years, detracting from quality of life, both for survivors<sup>3</sup> and their caregivers.<sup>10</sup> There is a lack of uniform cognitive testing for cardiac arrest survivors before they are discharged from the hospital, thus, it is unknown if the etiology of the cardiac arrest impacts their cognitive performance after successful resuscitation. This thesis will determine the association between the etiology of cardiac arrest and resulting cognitive impairment in survivors in Pittsburgh, PA, using one of the largest databases of post-arrest impairment assessments assembled to date.

## **1.1 Background – Cardiac Arrest**

Cardiac arrest occurs for a variety of reasons, but the end-result is the same: the heart stops pumping blood throughout the body, cutting off the oxygen supply to the brain, heart, and other vital organs. Within minutes, this oxygen deprivation can cause irreversible brain, heart, and cell damage and can quickly progress to death. Cardiac arrest creates heterogeneous illness patterns after successful resuscitation, and even with treatment, those who survive can suffer from a myriad of complications, including resuscitation-related injuries, such as broken ribs, seizures, abnormal liver function, septicemia, pneumonia, renal failure, hemorrhage, and respiratory distress.<sup>11</sup>

### **1.1.1 Scope of the Problem – Cardiac Arrest Incidence and Outcomes**

Cardiac arrest is a significant public health issue both worldwide and in the United States. It is responsible for the deaths of over 17 million people worldwide each year.<sup>12</sup> Annually in the United States, an estimated 350,000 to 420,000 people suffer from an out-of-hospital cardiac arrest (OHCA)<sup>2,13,14</sup> and more than 209,000 people suffer an in-hospital cardiac arrest (IHCA).<sup>15</sup> Survival rates vary depending on the location of the cardiac arrest, with approximately 8-10% of victims surviving an OHCA,<sup>2,14</sup> and an estimated 9% will survive with good neurological outcome.<sup>16</sup> IHCAs have a survival rate that is estimated to range 25-40% with varying neurological outcomes.<sup>15,17</sup>

The stark difference in survival rates between OHCA and IHCA may be attributed at least in part to the amount of cardiovascular “downtime” a patient experiences: that is, how long their heart has been stopped and blood flow to the brain has been interrupted before cardiopulmonary resuscitation (CPR) is started. The average time to CPR initiation in OHCA varies geographically

and is estimated to take at least six minutes for basic life support provided by police officers to reach victims;<sup>18</sup> this can be decreased to an average of two minutes if lay bystanders intervene.<sup>19</sup> Despite mass training and public health initiatives, average bystander CPR response rates remain low nationwide. The American Heart Association estimates that approximately 46.1% of OHCA receive lay bystander intervention;<sup>15</sup> however, large OHCA registry studies have put this estimate closer to 33.3-38.5%.<sup>20-21</sup> The amount of time for trained medical professionals to reach OHCA patients also varies by location. It is estimated that emergency medical services (EMS) reach patients in an average of six to nine minutes after 911 has been contacted, but this ranged from five to thirty minutes depending on geographic region.<sup>19</sup> This cannot account for downtime before the patient was found if the OHCA was unwitnessed, which is estimated to occur in 25% of OHCA.<sup>22</sup> IHCA may have much shorter downtime because patients may be continuously monitored, trained medical professionals and equipment are nearby, and standby teams are in place if alerted that a patient has arrested nearby.

Both OHCA and IHCA are often complicated by preexisting comorbidities, such as previous myocardial infarction, history of heart failure, and chronic obstructive pulmonary disease,<sup>23</sup> all of which combines to make survival, and particularly survival with intact neurological status, rare.

### **1.1.2 Pathophysiology of Cardiac Arrest Etiologies**

Cardiac arrest may arise from one of many etiologies and can be the terminal result of a number of different disease or injury states. The majority of cardiac arrests occur outside the hospital, with approximately 75% being OHCA.<sup>24</sup> In a recent study, cardiac arrests occurring in all locations received cardiac catheterization in 40% of cases; 34% of patients in this study later

required an implanted cardioverted-defibrillator.<sup>25</sup> Another study found that approximately 26% of all arrests treated at a single center were attributable to cardiac causes.<sup>26</sup> IHCA's are caused by cardiac etiologies in approximately 50-60% of cases and respiratory etiologies in 15-40% of cases.<sup>27</sup> Traumatic cardiac arrests are highly lethal but are only estimated to account for 3% of OHCA's.<sup>28</sup>

#### **1.1.2.1 Cardiac Etiology**

Cardiac arrest due to presumed cardiac etiology is typically attributed to sustained ventricular fibrillation or ventricular tachycardia as the terminal result of cardiovascular disease. Specific underlying causes of a cardiac etiology arrest are structural heart disease, including coronary artery disease exacerbated by atherosclerosis, or electrical dysfunction.<sup>29-30</sup> In some cases, notably those who are not considered to be at high risk, the first symptom of cardiac health issues is sudden cardiac death.<sup>30</sup> Overall, approximately 65-70% of cardiac etiology arrests that resulted in death were attributed to coronary artery disease.<sup>31-32</sup>

The physiological pathway for cardiac etiology arrest varies but can be simplified to the development of heart disease throughout the lifespan, which causes the accumulation of plaque on the interior of the arteries with possible co-occurrence of hardening of the coronary arteries, resulting in reduced or obstructed blood flow to the heart. This weakens the heart muscles and can kill cardiac myocytes, impairing the heart's ability to pump and interrupting the pacemaker cells' activity, finally resulting in electrical dysfunction and cessation of cardiac activity.<sup>30</sup> The survival rate for this type of cardiac arrest depends on the location of the arrest: for OHCA, the survival rate hovers around 12%, but increases to 24.8% in IHCA's that have direct access to a catheterization laboratory, thrombolytic medications, and mechanical support devices.<sup>15</sup>

### **1.1.2.2 Respiratory Etiology**

Several different mechanisms can cause a cardiac arrest due to respiratory etiology, but all mechanisms result in asphyxia. These mechanisms include, but are not limited to: drowning, airway obstruction (such as choking or hanging), inflammatory response (anaphylaxis), aspiration, blood clots, seizure, and drug-induced apnea (sedative, anesthetic, or narcotic overdose). All mechanisms prevent gas exchange from the upper airway to the alveoli of the lungs, which affects oxidative metabolism in vital organs.<sup>33</sup> This hypoxia, coupled with hypercapnia, causes severe acidosis and deteriorates cardiac function, resulting in bradycardia that may devolve into pulseless electrical activity or asystole, rather than a shockable rhythm, due to the disruption of energy metabolism from reduced oxygen levels in the blood.<sup>34</sup> Asphyxial cardiac arrests are more common in pediatric populations than in adults, and brain death is a common outcome. Survival is dismal. While approximately 44% of adult patients survived to hospital admission, only 30% survived the first 24 hours, and declined to 6% who survived to six months. In one study, zero patients who required more than 15 minutes of resuscitative efforts survived to six weeks after their cardiac arrest.<sup>35</sup>

### **1.1.2.3 Traumatic Etiology**

Cardiac arrest due to trauma has a historically poor outcome. This is due to the immediacy, severity, and relative irreversibility of the arrest etiology in the out-of-hospital setting. Traumatic cardiac arrests are often the result of exsanguination or injuries to the central nervous system, and the majority of these deaths occur within the first two hours of the injury.<sup>36-37</sup> In cases of exsanguination, the physiology of the arrest is generally as follows: following injury, the patient's heart continues to pump blood throughout the body and exits through the open, uncontrolled wound via damaged artery or vein. This reduces the amount of oxygenated blood that is returned



to the heart through the coronary arteries and the brain becomes underperfused. The heart cannot continue to pump once the body has run out of oxygenated blood to circulate. Cardiac activity ceases once the blood volume has decreased below a certain point if the bleeding is not stopped and if the patient's blood volume is not restored.<sup>38</sup>

In cases of blunt force injuries to the central nervous system, the patient's brain may have suffered damage severe enough to prevent innervation from reaching the cardiac and respiratory muscles, causing cardiac activity to cease. In cases of blunt force injuries to the chest, the patient's heart may have sustained direct physical damage such as a puncture, preventing its ability to pump blood throughout the body. Cardiac activity ceases.<sup>39</sup> Blunt force injuries may also coincide with hemorrhagic injuries, compounding the issue and making survival, particularly survival with intact neurological status and desirable cognitive outcomes, highly unlikely. In cases of closed-chest prehospital traumatic cardiac arrest, the survival rate has been estimated to range as low as 0-2.6%.<sup>28,38,40</sup>

### **1.1.3 Biological Plausibility: Etiologic Relationship to Neurologic Status**

Cardiac arrest etiologies are loosely associated with presenting rhythm. Respiratory arrests often present in bradycardic and then asystolic rhythms<sup>34</sup> while cardiac etiologies may present more often as shockable initial rhythms due to myocardial electrical dysfunction.<sup>30</sup> Differences in physiologic mechanisms of arrest result in unique organ injury phenotypes in rats.<sup>41</sup> Anoxic cardiac arrests had worse neurologic injuries compared to cardiac etiology arrests. This was due to increased oxidative injuries in three regions of the hippocampus and the cerebellar cortex as well as increased neuronal loss in two regions of the hippocampus and the cerebellar cortex.<sup>41</sup> Additionally, cardiac etiology arrests in humans were associated with less severe initial brain

injury and better functional status at discharge compared to anoxic cardiac arrests, which corroborates the findings in rats.<sup>41</sup>

#### **1.1.4 Complications of Cardiac Arrest**

The complications of cardiac arrest are wide reaching, often intersecting, and can be difficult to measure in isolation. The most obvious complication of cardiac arrest is the heightened risk of death during resuscitation and immediately after the patient regains pulses.<sup>42</sup> Assuming the patient survives to hospital admission, there are various medical complications that must be addressed, including but not limited to post-critical illness syndrome, post-intensive care syndrome, tracheal stenosis, delirium, reduced mobility, muscle weakness and wasting, inflammation, rib fractures, visual disturbances, and fatigue,<sup>43</sup> which may not resolve after hospital discharge after the acute cardiac arrest event.<sup>44</sup>

#### **1.1.5 Non-Fatal Outcomes of Cardiac Arrest**

##### **1.1.5.1 Functional Impairment**

Functional impairment is crudely defined as having reduced abilities or independence in activities of daily living.<sup>45</sup> This is a common concern for survivors of cardiac arrest, their families and their caregivers. Large registries have focused on measuring functional impairments and have estimated that 18% of IHCA survivors and 40% of OHCA survivors experience functional impairments severe enough to prevent their return to work and normal activities of daily living.<sup>46</sup> Functional impairment is assessed using exams such as the Cerebral Performance Category-Extended (CPC-E) and the Modified Rankin Scale (mRS). These exams use 5- or 6-point scales

to assess global functioning, with higher scores indicating increased impairment or death. These exams cannot detect more subtle cognitive deficits that may impact a cardiac arrest survivor's ability to return to a normal quality and style of life. It is possible for patients to perform very well on functional impairment assessments yet still suffer from cognitive deficits following cardiac arrest.<sup>47</sup>

#### **1.1.5.2 Cognitive Impairment and Assessment**

Cognitive impairment is defined as having problems with short or long-term memory, concentration, or decision-making on the mild end of the spectrum to losing the ability to write, speak, understand others, and ultimately the ability to live independently in the most severe cases.<sup>48</sup> Cognitive impairment is diagnosed when the patient scores at or below a preset threshold on an exam specifically designed to assess cognition, such as the Mini Mental State Exam (MMSE), the Computer Assessment of Mild Cognitive Impairment (CAMCI), and the Montreal Cognitive Assessment (MOCA). Table 1 shows a selection of cognitive exams used in cognitive impairment literature stratified by varying patient population type.

Issues with cognition differ from functional impairment, in that a cognitively impaired individual may be functionally unimpaired and therefore physically able to return to their normal, pre-medical event level of activity, such as going to work or driving. However, functional exams should not be used as tools to assess patients' cognition. Physical impairments can impact a patient's functional abilities, even if their cognition was not affected. For example, patients with severe edema of the hands due to impaired vascular function can experience a decrease in their functional motor skills, which would have a negative impact on their cognitive exam score, due to their inability to manipulate a pen or pencil for written exams.

### **1.1.5.3 Cognitive Impairment after Cardiac Arrest**

Cognitive impairment, with short term, episodic memory loss in particular, is a common complaint for many cardiac arrest survivors. The causal pathway is not fully understood, and it is unlikely that the resultant brain damage is due to any single mechanism or pathway.<sup>12</sup> It is theorized that primary brain damage occurs both during the cessation of blood flow during the cardiac arrest itself, and secondary injury results from reperfusion during resuscitation and when blood flow is restored.<sup>12,34</sup> This increase in oxidative stress activates a cascade of cytokines, chemokines and other molecules that amplifies the reperfusion injury.<sup>49</sup> Secondary brain injuries are caused after successful resuscitation by ongoing ischemia, cerebral hypoperfusion, edema, autoregulatory failure, and seizures that can occur in the hours and days after the initial arrest event.<sup>12</sup>

It is thought that parts of the brain that are more sensitive to oxidative stress and injury, and specific impairments may be attributed to damage in pinpointed brain regions. Chronic memory loss may stem from global brain volume loss or lesions and atrophy in specific brain areas. The CA1 field of the hippocampus is notably sensitive to hypoxia, and damage caused by cardiac arrest may be responsible for resulting amnesia.<sup>50-51</sup>

Data on the frequency of cognitive impairment following cardiac arrest are not complete. Cognitive outcomes in cardiac arrest survivors are not uniformly measured across all healthcare systems and are impacted by a variety of factors. There are currently no cognitive exams or batteries of tests specifically designed to assess cardiac arrest survivors' unique patterns of cognitive impairment, and all tests used thus far have been borrowed from other fields, such as dementia research; these tests may not be adequately calibrated for the unique needs of cardiac arrest survivors.<sup>52</sup>

Another common complication of surviving a cardiac arrest that impacts exam proctors' ability to provide cognitive assessments is increased patient fatigue. One study estimated that up to 55% of survivors experienced severe fatigue (as determined by the Fatigue Severity Scale) even a year after hospital discharge. It was speculated that fatigue coincided with cognitive impairments and emotional problems attributed hypoxic brain damage that occurred during the cardiac arrest event, which could negatively impact a patient's score.<sup>44</sup>

### **1.1.6 Gaps in the Literature and Proposed Project**

As previously mentioned, cognitive outcomes are not uniformly assessed prior to hospital discharge in the United States. The physicians and scientists working with the Post Cardiac Arrest Service (PCAS) at the University of Pittsburgh routinely assess survivors and have been monitoring cognitive outcomes with various cognitive exams at UPMC Presbyterian and UPMC Montefiore hospitals since 2010. At this time, a database with over 300 cognitive exams is available, and includes both functional and cognitive assessments using the mRS, the CPC-E, the MMSE, the CAMCI, the 41 Cent Test, and the MOCA.

The database contains multiple exams spanning entire years from 2010 to the present and provides the opportunity to match patient exam scores with arrest etiologies. The setup of the MOCA, which provides an overall score, as well as subscores for different areas of cognition such as attention and executive function, sheds light on an unexplored link between cause of cardiac arrest and the measurable impact on cognitive function after resuscitation. Identifying this link will help healthcare providers give patients the support they need as they transition out of the hospital and back to their homes or other care facilities.

This thesis will address the identified gaps in the literature with the following aims and hypotheses.

**Aims:**

1. To determine the prevalence of each etiology category of cardiac arrest in the PCAS database: cardiac, respiratory, trauma, and other/unknown
2. To assess the relationship between etiology and MOCA
  - a. To assess the relationship between cardiac arrest etiology and overall MOCA
  - b. To assess the relationship between cardiac arrest etiology and specific domains of the MOCA
  - c. To assess the relationship between cardiac arrest etiology and a binary (impaired vs. not-impaired) assessment of the MOCA
3. To explore if the relationship is modifiable by age, sex, or other patient demographics or characteristics

**Hypotheses:** Cardiac arrest etiology will impact cognitive exam score and patient demographics and characteristics will modify that relationship. Specifically, traumatic and respiratory arrests will exhibit more severely impaired cognition when compared to cardiac etiology of arrest, and variables including age, sex, witnessed status, length of time in the intensive care unit (ICU), coma status on emergency department (ED) arrival, length of hospital stay, and length of time from initial arrest to cognitive assessment will modify this relationship.

## **2.0 Methods**

### **2.1 PCAS Service and Patients**

The Post Cardiac Arrest Service (PCAS) of UPMC has been providing specialized care to cardiac arrest patients since 2005. The service is made up of ten physicians, one critical care physician assistant, and three cognitive examination proctors. Between January 1, 2010 and November 12, 2019, PCAS has seen approximately 2,724 patients and averages 303 patients per year. The analyses were limited to the 1,999 patients who were seen by the PCAS between 2012 and 2018. In our dataset, patients ranged in age from 14 to 96 years, with a mean (SD) age of 59.3 (16.8) years. Approximately 58.1% of PCAS patients were male. Approximately 76.6% of arrests occurred out-of-hospital, and the overall survival to hospital discharge rate was 37.6%.

#### **2.1.1 Arrest Etiology Determination and Categorization**

Etiology of arrest was determined via medical record review of all patients who were seen by the PCAS between January 1<sup>st</sup>, 2012 and December 31<sup>st</sup>, 2018 at UPMC Presbyterian or Montefiore. Etiologies of arrest were determined through medical record review by Dr. Jonathan Elmer, MD, a critical care specialist at the University of Pittsburgh, and his research assistant Mr. Niel Chen, BS, using methods previously published;<sup>26</sup> in short, reviewers used data available in the prehospital patient care report (written by emergency medical services) and electronic medical records (from the hospital admission), which include toxicology screens, physical examination, laboratory specimen results, and nursing care notes, among others to categorize arrests into one of

fourteen etiologies. See Figure 1 for a breakdown of etiology category assignment in accordance with previously published methodology.<sup>26</sup> All cases were assigned etiologies by Dr. Elmer and Mr. Chen in accordance with the previously published methodology.<sup>26</sup>

Etiologies were then stratified into four main categories: cardiac etiology, respiratory etiology, traumatic etiology, or other/unknown etiology. For the purposes of this study, etiologies were analyzed in two different ways:

1. Cardiac, respiratory, trauma and other/unknown were compared to each other
2. Trauma (including exsanguination) was excluded from all analyses due to the low probability of patients surviving traumatic cardiac arrest with intact neurological status.

Due to the pathophysiology of traumatic cardiac arrests, the overall n for the trauma group was not commensurate with the number of patients in other categories. However, traumatic cardiac arrest characteristics were too dissimilar from the other/unknown category to be folded into that group, so traumatic etiology was analyzed as its own group and excluded from other analyses to assess what impact that etiology had on the overall results.

Cardiac etiology broadly encompassed all arrests with a suspected origin of cardiac nature. This included: acute coronary syndrome, arrhythmia secondary to cardiomyopathy, left ventricle failure, right ventricle failure, intrinsic arrhythmia, heart disease, and metabolic derangement. Respiratory etiology included all patients with a suspected origin that was asphyxial in nature, including: respiratory, airway obstruction, and toxicological etiologies. Traumatic etiology included all arrests categorized under trauma and exsanguination. All other arrests with other etiologies or those with indiscernible etiologies were categorized into a third group, other/unknown. MOCA score sheets were matched to the etiologies of arrest database using a



unique patient identifier that was kept separate from any personally-identifying information for the patients' security.

#### **2.1.1.1 Cognitive Examinations**

The service implemented regimented neurocognitive testing in 2010, originally consisting only of the MMSE and the CAMCI, a computerized exam designed to evaluate cognitive impairment associated with dementia.<sup>53</sup> In 2012, the service added the MOCA and the 41 Cent Test, the latter of which was developed by the PCAS, to the testing regimen.<sup>52</sup> The testing regimen has been modified in the intervening years, but the MOCA has been routinely administered since its addition to the protocol, and provides an overall score as well as cognitive domain subscales, such as Executive Function and Language. It is widely available online for free. Based on prior published work from the University of Pittsburgh and the PCAS, the MOCA provides an ideal middle ground: not as time-consuming and in-depth as the CAMCI, but more detailed than the 41 Cent Test and the MMSE. Due to the ease of administration, which takes no more than 15 minutes to complete, longevity of use in our patient population, relative depth of knowledge gained from the MOCA, and its widespread use in other diseases as a reliable measure of cognitive function,<sup>54-57</sup> this exam was chosen as the basis of this thesis. The MOCA has been validated in other disease states, including frontotemporal dementia<sup>58</sup> and vascular dementia.<sup>59</sup>

The exams given by the PCAS are unique in that they are administered prior to hospital discharge. Other studies in this area of cardiac arrest survivors often wait months or even years after hospital discharge to assess long-lasting cognitive impairment, which has been estimated to last for six months to several years.<sup>3,6,8</sup> The PCAS cognitively examines patients before hospital discharge, as this provides a window for intervention that is missed if testing is delayed by weeks or months after patients are sent home.

Patients seen by the PCAS were considered eligible for voluntary cognitive exam screening after they are deemed awake, alert, and oriented by the physicians of the PCAS, who administered the MMSE. Once the patient performed satisfactorily on the MMSE (approximately 20 points minimum out of a possible 30 or 66.7%, or by physician judgement), cognitive exam proctors were then sent to see the patient for further testing. All proctors received the same training on how to administer these exams and administered the exams in pairs during the training period to reduce variability in style of exam administration. All patient participation was voluntary, and patients were given the option to end their participation at any point in the testing sequence.

Cognitive testing occurred between 24 and 72 hours after the patient had been discharged from the intensive care unit (ICU) but before they were released from the hospital to their homes, a rehabilitation facility, or to a skilled nursing facility. Due to varying courses of treatment, patients may have received cognitive testing between a few days to weeks after their initial cardiac arrest. Patients were given a battery of cognitive exams, including the CPC-E, the 41 Cent Test, and the MOCA and were given supporting material prior to discharge. The cognitive exam proctors offered the same battery of tests and patients were given the same supporting materials regardless of the cause of their arrest, length of stay in the hospital, or any other patient characteristic or demographic (i.e., any patient age). The exams were administered in order of increasing difficulty and length: CPC-E was given first, followed by the 41 Cent Test, culminating in the MOCA. If the testing session was interrupted, or if the patient became upset or wished to cease testing, the proctors ended the session. It was possible for proctors to revisit the patient in the following days to try to complete the exam set unless the patient had expressly stated that they did not wish to continue testing. In this thesis, all attempted and completed MOCA exam sheets were reviewed, and overall scores, as well as subscales for each domain, were recorded, including:

visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall, and orientation.

#### **2.1.1.2 Medical Record Review – Modified Rankin Scale and MMSE**

The MMSE was routinely used as a screening tool by the PCAS for survivors of all-cause cardiac arrest. However, this score was not documented within the cognitive exams database. A medical record review was performed on all 1,999 PCAS patients between 2012 and 2018. The Modified Rankin Scale (mRS), a functional outcomes indicator, was assigned to all patients by a research specialist via medical record review to determine if the patient was bedridden (mRS=5) or walking (mRS ≤4) on day of discharge from the hospital. Ambulatory patients' records underwent further review to determine mRS 0-4 status based on the amount of assistance needed in completing basic activities of daily living. Medical record review was then performed by the author for patients scoring 0-4 on the mRS to ascertain MMSE status, as those patients were deemed functionally able to complete cognitive assessments; an mRS score of 5 indicated severe illness and mRS of 6 indicated death. See Figure 2 for a flow diagram from patient enrollment to MOCA status.

MMSE scores were inconsistently reported within the medical record and for the purposes of this study were recorded as total, reconstructed, missing, or unknown. Total scores were reported by physicians and could range for any possible points out of 30, with scores less than 30 possible points being truncated for various reasons. In records where no overall score was reported, any evidence of the exam being conducted was recorded. Physicians often reported sections of the MMSE; if sections were found in the medical record, patient scores were reconstructed using those sections. See Table 2 for examples of this reconstruction method. Physicians could also report that the MMSE was done, but no scores or sectional scores were reported. These were labeled as

completed but missing and analyzed as part of the unknown group. If there was no mention of the MMSE in the medical record, it was labeled as unknown MMSE status and these data were analyzed with the completed but missing patients.

### **2.1.1.3 MOCA Data Manipulation**

The MOCA is unique in the testing regimen in that it yields an overall score as well as scored subcategories. The data were analyzed using 26 out of 30 points as the threshold for normal cognition, as this cutoff has been used in this population previously.<sup>52</sup> Scores were converted to percentages, using 26/30 or 86.7% as the threshold for normal cognition, in order to include patients whose MOCA scores were truncated to less than 30 total points. Typically, scores were truncated to a total of 25 possible points rather than 30 points for functional reasons, including if the patient was visually impaired and did not have access to their glasses or contacts or if they had issues physically manipulating a pen, and therefore were either unable to see the visuospatial/executive portion of the exam or unable to complete the required drawing due to gross physical restrictions. The MOCA was done in its entirety in 166 (86.5%) patients.

Using the 86.7% cutoff, the continuous score variable was converted into a dichotomous variable (normal/abnormal cognition). The dichotomous score variable was then compared between etiology groups using the categorical etiology variable: Cardiac, Respiratory, Trauma, or Other/Unknown; logistic regression was used for this analysis. Additional analyses compared percentage score as a continuous variable and raw subcategory scores to the categorical etiology variable using linear regression. These analyses included any truncated scores as well.

#### **2.1.1.4 Statistical Methodology**

After plotting the time interval data, median and interquartile ranges were reported to reduce the influence of outliers. To determine if there was an association between hospital length of stay or ICU length of stay with whether patients were given the MMSE or MOCA, two-sided t-tests were performed for length-of-stay data and Kruskal-Wallis tests were performed to assess variance in length-of-stay. T-tests were also used when means of groups were compared for other patient characteristic data. To determine if etiology category was predictive of continuous MOCA score, linear regression was used. When MOCA score was converted to the binomial abnormal or normal cognition and compared to etiology category, logistic regression was used. Stepwise regression was performed to assess the influence of patient demographics on key outcomes and collinearity was tested for using linear regression. Results are reported as mean (SE) or median (IQR) where appropriate. For all statistical tests, an alpha level of 0.05 was used to determine significance. Stata SE (v. 16, College Station, TX) was used for all statistical analyses.

### **3.0 Results**

#### **3.1 Etiology and Survival**

Between January 1<sup>st</sup>, 2012 and December 31<sup>st</sup>, 2018, the PCAS evaluated 1,999 cardiac arrest patients, of whom 750 (37.6%) survived to hospital discharge. Of the total 1,999 patients, 662 (33.12%) were classified as cardiac etiology, 556 (27.81%) were classified as respiratory etiology, 96 (4.80%) were classified as traumatic etiology, and 685 (34.27%) were classified as other/unknown etiology. Survival rates for each etiology are as follows: cardiac 51.7%; respiratory 31.5%; trauma 21.9%, other/unknown 31.1%. Using logistic regression, all etiologies were significantly less likely to survive when compared to the cardiac etiology ( $p < 0.01$  for all).

#### **3.2 Cognitive Exams**

Patients who scored 0-3 points out of a possible 6 on the mRS were considered functionally unimpaired enough to be given the MMSE and those who scored a 4 on the mRS had borderline impairment. Those who scored a 5 on the mRS were too severely ill to take the MMSE and those coded as an mRS of 6 were dead. A total of 529 patients scored 0-4 on the mRS. The medical record review yielded 176 complete MMSE scores, 96 reconstructed MMSE scores, and 257 with missing or unknown exam status. The MOCA was later given to 192 patients. See Table 3 for the distribution of etiologies and demographic information for all cardiac arrest survivors. Of note, the respiratory arrests were on average 7.65 years younger than cardiac etiology arrests, but there were

no other significant differences between the groups with respect to age or sex. Table 4 shows etiology and demographic information for MOCA participants. There were no differences with respect to age and sex between the etiologic categories when restricted to MOCA participants only.

See Table 5 for etiology breakdown by mRS score. This table includes all PCAS patients; the majority were deceased at discharge (62.3%). Approximately 1.21% were discharged with no symptoms, and 27.7% were discharged with an mRS ranging 0-4, indicating mild to moderate impairment across all etiologies. Traumatic arrests had the highest percentage (78.1%) of all the etiologies in the mRS 6 (dead) group, compared to 48.4% in the cardiac etiology group.

Table 6 shows etiology breakdown for patients who did and did not get a MOCA when restricted to patients with good functional status (mRS 0-4). Using a chi-squared test, the proportions of each etiology category did not differ by MOCA status ( $p=0.149$ ).

### **3.3 Length-of-Stay Analyses**

Time to intervention data were strongly positively skewed (see Figure 3 for time to exam administration and Figure 4 for length-of-stay histograms). To minimize the influence of outliers, median and interquartile range (IQR) are reported for time interval results.

The median (IQR) hospital length of stay for all patients was 5 (2-13) days, and the length of stay ranged from 0 to 185 days. The median (IQR) length of stay in the ICU for all patients was 3 (1-7) days, and the length of stay ranged from 0 to 167 days. The median (IQR) time from initial cardiac arrest to MMSE was 5 (3-10) days and the median (IQR) time from initial cardiac arrest to MOCA was 7 (4-11) days.

Length-of-stay estimates for all patients, for survivors only, for all non-traumatic patients, and for non-traumatic survivors only by MMSE and MOCA status are given in Table 7, and length of hospital stay by survival status is shown in Figure 5. As the time interval data were non-parametric, medians are reported throughout: hospital length-of-stay was significantly longer in patients who took the MMSE (MMSE 11 days vs. no MMSE 4 days,  $p=0.00$ ) and in patients who took the MOCA (MOCA 10 days vs. no MOCA 4 days,  $p=0.00$ ) when all patients were included; however, this finding was reversed when only survivors were included in the analysis. Hospital length of stay was significantly longer in patients without the MMSE (MMSE 11 days vs. no MMSE 15 days,  $p=0.00$ ) and in patients with the MOCA (MOCA 10 days vs. no MOCA 15 days,  $p=0.00$ ) when analyses were restricted to all-etiology survivors. Hospital length of stay was significantly longer in all non-traumatic patients who took the MMSE (MMSE 11 days vs. no MMSE 4 days,  $p=0.00$ ) and but this was reversed when traumatic non-survivors were excluded (MMSE 11 days vs. no MMSE 15 days,  $p=0.00$ ). In all non-traumatic patients, regardless of survivorship, those who took the MOCA had a significantly longer hospital length of stay (MOCA 10 days vs. no MOCA 4 days,  $p=0.00$ ), but when these analyses were restricted to non-traumatic survivors only, patients who did not take the MOCA had a significantly longer stay (MOCA 10 days vs. no MOCA 15 days,  $p=0.00$ ).

When all patients were included, patients who took the MMSE had a significantly longer length of ICU stay (MMSE 5 days vs. no MMSE 3 days,  $p=0.00$ ), as did patients who took the MOCA (MOCA 4 days vs. no MOCA 3 days,  $p=0.00$ ). These findings were reversed when the analyses were restricted to all etiology survivors only: ICU length of stay was significantly longer in patients who did not take the MMSE (MMSE 5 days vs. no MMSE 7 days,  $p=0.00$ ) and those who did not take the MOCA (MOCA 4 days vs. no MOCA 7 days,  $p=0.00$ ).



Analyses were then restricted to all non-traumatic cases, regardless of survivorship status. Similar to earlier all-survivor, all-etiology findings, patients who took the MMSE had a significantly longer length of ICU stay (MMSE 5 days vs. no MMSE 3 days,  $p=0.00$ ), as did patients who took the MOCA (MOCA 4 days vs. no MOCA 3 days,  $p=0.00$ ). Again, these findings were reversed when analyses were restricted to non-traumatic, survivor-only cases: ICU length of stay was significantly longer in patients who did not take the MMSE (MMSE 5 days vs. no MMSE 7 days,  $p=0.00$ ) and those who did not take the MOCA (MOCA 4 days vs. no MOCA 7 days,  $p=0.00$ ).

### **3.4 Patient Demographics and Characteristics**

Age, sex, witnessed status, arrest location (in-or-out of hospital), and coma on ED arrival were reliably recorded for this dataset (defined as recorded for greater than 90% of dataset). Patients who took the MOCA were significantly younger (mean 56.3 vs. 59.6 years,  $p=0.01$ ), more likely to have arrested out-of-hospital (83.3% vs. 76.3%,  $p = 0.03$ ), more likely to have a shockable first rhythm (49.5% vs. 25.5%,  $p = 0.00$ ), and were more likely to be non-comatose on ED arrival (37.8% vs. 79.7%,  $p = 0.00$ ) than those who did not take the MOCA. Sex and witness status were not significantly different between MOCA and non-MOCA patients (sex: 56% vs. 58%,  $p = 0.56$ ; witnessed status: 56.2% vs. 61.9%,  $p = 0.29$ ).

Education was not reliably recorded for this dataset. For patients without any cognitive exams, there was no recorded education status. The MOCA is designed such that one point is added to the overall scored points if the patients had less than 12 years of education. While the exam proctors are required to ask patients about their educational status prior to beginning the

MOCA and would adjust the overall score if needed, education status was only documented in 114 of the 192 (59.4%) MOCA sheets. The breakdown by educational attainment is given in Table 8. Using linear regression, only having an educational status of “some high school” was predictive of poorer performance on the MOCA ( $p = 0.036$ ). Increased educational attainment had higher MOCA scores, but this finding was not statistically significant.

### **3.5 Arrest Etiology and MOCA Overall Score**

Mean (SE) MOCA score for all etiologies was 72.8 (1.1) percent, indicating abnormal cognition. The mean scores by etiology are given in Table 9 and the distribution of scores is shown in Figure 6. The scores are normally distributed with a negative skew and a peak around 75%, below the cut-off for normal cognition. There were no obvious outliers. MOCA percent score distribution by etiology is shown in Figure 7 with the overall score as a comparator for each etiology.

When MOCA was categorized as a continuous percentage score and linear regression was used, MOCA score was not significantly associated with arrest etiology ( $p=0.200$ ). Using cardiac etiology as the reference, respiratory cardiac arrest scored on average 5.47 points lower, trauma scored 4.6 points lower, and other/unknown etiology scored 3.3 points lower; however, none of these findings were significant ( $p=0.07, 0.56, 0.21$ , respectively).

When MOCA was categorized as a binomial indicator of abnormal/normal cognition and using logistic regression, respiratory etiology were 2.5 times more likely to exhibit abnormal cognition compared to cardiac etiology. Trauma etiology was 3.4 times more likely to exhibit abnormal cognition compared to cardiac etiology, and other/unknown etiology was 2.2 times

more likely to exhibit abnormal cognition compared to cardiac etiology. All of these findings were statistically significant ( $p=0.00$ ,  $0.02$ ,  $0.00$ , respectively – see Table 10).

### **3.5.1 Arrest Etiology and MOCA Subscales**

The MOCA is broken down into seven subscales: visuospatial/executive (5 points), naming (3 points), attention (6 points), language (3 points), abstraction (2 points), delayed recall (5 points), and orientation (6 points), but there is no listed cut-off for a passing score in each category. These data were analyzed as a continuous variable only. For all MOCA participants regardless of etiology, the mean (SE) points per subcategory were: visuospatial/executive 4.2 (0.7), naming 2.8 (0.04), attention 4.7 (0.1), language 2.2 (0.1), abstraction 1.9 (0.02), delayed recall 1.7 (0.1), orientation 5.2 (0.1). Delayed recall was the most severely impacted domain, with patients recalling an average of 1.67 of the 5 words at 5 minutes. See Table 11 for a breakdown of subscores by etiology. Using binomial linear regression, respiratory etiology performed significantly worse than cardiac etiology in two domains: attention (4.11 vs. 4.9 points,  $p=0.004$ ) and language (1.89 vs. 2.27,  $p = 0.04$ ). Other comparisons were not significantly different.

## **3.6 Patient Demographic Modifiers**

Linear and logistic regression analyses were repeated while controlling for patient age, sex, witnessed status, length of time in the ICU, coma status on ED arrival, overall length of time in the hospital, and length of time from initial arrest to cognitive assessment. When controlling for

age, sex, witnessed status, coma status, and length of time in the ICU, the statistical findings were unchanged (Multivariate Model 1, Table 12). However, including time from arrest to MOCA and separately the total length of hospital stay in the model caused the binary normal/abnormal cognition difference between the etiologies to become insignificant (Multivariate Model 2, Table 13). The mean length of time from initial arrest to MOCA administration was 9.2 days, and the mean length of time in the hospital was 9.6 days. A hospital stay of greater than 9 days may obscure any influence etiology may have over cognition scores. Collinearity between etiology and time to cognitive exam was ruled out using linear regression ( $p=0.22$  overall;  $p=0.64$  for respiratory,  $p=0.47$  for trauma,  $p=0.185$  for other/unknown using cardiac as the reference); however, increased time to MOCA administration was significantly associated with decreased MOCA percentage score (coefficient  $-0.29$ ,  $p=0.02$ ). When patient age, sex, witnessed status, coma status and ICU length of stay were added to the regression model comparing subscales and etiology, attention remained significantly impacted in the respiratory etiology (Table 14). However, once time to MOCA administration was added into the model, all statistically significant associations were nullified.

### **3.7 Trauma-Excluded Analyses**

Traumatic etiologies made up less than 5% of the entire dataset. However, as this etiology had unique mechanisms, it was hypothesized that this group would have unique characteristics that would prevent them from being folded into the other/unknown etiology category. To see what effect keeping these cases as their own category had on our results, secondary analyses were performed that completely excluded the entire group.

Survival remained significantly worse in respiratory and other/unknown etiologies compared to cardiac ( $p < 0.01$  for both groups). After excluding the traumatic arrests, mean overall MOCA score remained at 72.8%, and MOCA subscale scores were unchanged from previous analyses, indicating that the traumatic etiology group did not have a particularly large influence over the cognitive exam results. Statistical associations between MOCA score and etiology did not change. Respiratory and other/unknown etiology groups still performed more poorly than the cardiac group when MOCA scores were analyzed as a continuous variable, but none of these findings were significant (respiratory: coefficient -5.47,  $p=0.073$ ; other/unknown: coefficient -3.31,  $p=0.215$ ). MOCA score as a binary indicator of cognition remained significantly associated with etiology: respiratory arrests were 2.53 times more likely ( $p=0.00$ ) and other/unknown etiology arrests were 2.17 times more likely ( $p=0.00$ ) to have abnormal cognition compared to cardiac etiology patients. Patients who took the MOCA were still significantly younger than those who did not (mean 56.5 vs. 59.5 years,  $p=0.021$ ) and there was no difference in the percentage of males who were in the MOCA group vs. the non-MOCA group when the traumatic arrests were excluded (56% vs. 58%,  $p=0.59$ ); these findings are unchanged from previous analyses. Excluding the traumatic arrests did not change the proportion of witnessed arrests in the MOCA vs. non-MOCA group (55.8% vs. 61.2%,  $p=0.3272$ ). It does not appear that the traumatic etiology group exerted undue influence over any findings, likely due to their small overall sample size.

## **4.0 Discussion**

### **4.1 Major Findings**

The major finding of this study was that while etiology did not predict the MOCA score itself, respiratory, traumatic, and other etiology arrests were several times more likely to exhibit abnormal cognition than cardiac etiology arrest survivors. Regardless of etiology, the majority of cardiac arrest survivors with functional mRS scores who were given the MOCA exhibited abnormal cognition prior to hospital discharge. Respiratory arrests appeared to score significantly worse in language and attention subscales of the MOCA than other etiologies, and all etiologies had severe difficulties completing the delayed recall portion of the exam. However, these findings were made insignificant when time to MOCA administration and total length of stay were included in the statistical model. Increased time to MOCA administration was associated with decreased MOCA score, suggesting that timing has a larger influence over cognitive scores than etiology does in this patient population.

Due to the small number of traumatic arrest survivors relative to other etiologies, analyses were calculated after excluding them. The results were unchanged when traumatic arrests were excluded entirely, suggesting that the traumatic arrests exerted a very limited influence. We have included them in this study, as they are traditionally excluded from almost all other cardiac arrest studies. This study characterizes them and contributes to their body of literature.

Several length-of-stay analyses were also calculated after excluding non-survivors (Table 7). Early non-survival drove down the ICU and overall hospital length of stay estimates for those without cognitive exams, as they were critically ill and did not survive to examination. The median

length of stay for non-survivors was 2 days compared to a median of 14 days for survivors. The median time to both MMSE and MOCA was 5 days. When non-survivors were excluded, patients with MMSE and MOCA scores had significantly shorter ICU stays and significantly shorter overall hospital stays, regardless of etiology. Including non-survivors in these analyses did not affect the length of hospital or ICU stay medians for the patients with MMSE and MOCA scores, but their inclusion increased the median length of stay for patients without an MMSE or MOCA from 3 to 7 days in the ICU and 4 to 15 days in the hospital. As the majority of patients in the PCAS database did not survive, and survival is acutely necessary to take the MMSE and MOCA, survivorship should be considered when comparing length of stay.

Time from cardiac arrest to MOCA administration was plotted against MOCA percentile score (Figure 8). The data appear to show two trends: there is a cluster of scores between approximately 65-100% on the MOCA for patients who took the exam between 2 and 15 days post-arrest, and there is a positive linear trend starting at approximately 6 days and extending through 36 days where the MOCA score increases from 30% to 80%. This second, linear trend supports the hypothesis that MOCA scores increase significantly as patients are given time to recover from their cardiac arrest event, as well as from their time in the ICU. It is possible that testing patients within 24-72 hours after ICU discharge does not allow for associated delirium to dissipate, and that timing of the exam will overpower the effects of etiology on cognitive performance and impairment. It was not possible to determine with certainty if this was the case for participants in this study due to the low number of MOCA exams and varying times of administration with respect to cardiac arrest event. However, in the future, an implication of this finding would be to conduct a study where all participants would receive the MOCA at the same time point post-arrest, or to test all participants with the MOCA serially after ICU discharge to

account for the temporal improvement in scores. To understand the impact of etiology on cognition, it is imperative to first understand the influence of timing of exam administration; timing of exam administration must be standardized to account for this influence.

## **4.2 Biases**

The use of the MOCA patients as the population of interest introduced bias to this sample. Patients who took the MOCA were significantly younger, more likely to have arrested out-of-hospital, more likely to have a shockable first rhythm, and were more likely to be non-comatose on ED arrival than those who did not take the MOCA; however, sex and witness status were did not significantly differ between the MOCA and non-MOCA groups. Younger age, shockable first rhythm, and awake on arrival are beneficial factors and the patients who took the MOCA may have benefitted from these factors. These factors all limit generalizability of findings to the subset of cardiac arrest survivors who were functionally the least impaired. Those with more severe functional impairment may also benefit from in-hospital cognitive assessments, but were missed due to the assessment protocol of having a desirable mRS score and then being screened with the MMSE. Future work will assess the characteristics of patients who were too functionally impaired to be screened with the MMSE as they compare to those given the MOCA. Some additional patients were missed due to availability issues of the cognitive examination proctors who were attempting to conduct the MOCA with patients in the hospital prior to discharge. This was minimized by repeated attempts over several consecutive days to assess the patient prior to discharge, and was estimated to account for less than 5% of patients eligible for the MOCA.



Despite the generalizability of these findings being limited to cardiac arrest patients with the highest functional capabilities, it is worth noting that the study population still shows evidence of significant cognitive impairment. Extrapolating these findings to patients who were too sick to take the MMSE indicates severe impairment in the unassessed group as well.

In prior literature, OHCA survival was estimated at 8-12%, IHCA survival was 24-40%, respiratory arrest survival was 30% at 24 hours and 6% at six months, and trauma survival to hospital discharge was 0-2.6%. The survival rates in this study population varied from what has been reported in the literature. Patients who experienced an OHCA but were treated by PCAS had a survival to hospital discharge rate of 35.5%; IHCA patients treated by PCAS had a 43.6% survival rate. Cardiac etiology arrest in the PCAS service had a 51.7% survival rate. This was decreased to 31.5% survival for respiratory arrests, 21.9% survival for traumatic arrests, and 31.1% survival for other/unknown etiologies. The PCAS database's IHCA survival rate is commensurate with that of published studies, but the OHCA and etiology-specific survival rates are much higher. The PCAS database is subject to selection bias: it only includes data on IHCA patients and OHCA patients who survived to hospital admission. Patients who died prior to EMS arrival at the hospital were not included. This likely resulted in an increased survival to hospital discharge rate for all etiologies in the PCAS patient population compared to published studies that included all cases of OHCA, as the most severely sick and injured OHCA cases were not accounted for in the PCAS survival rate estimates.

### 4.3 Limitations

The sample size was limited and prevented more in-depth analyses, especially when considering the traumatic etiology group who took the MOCA (n=4). The reduced sample size underpowered this study and obscured statistical differences between the etiological groups.

Better capture of education status is needed in all patients to better elucidate the relationship between increased education level and MOCA score. Better capture of MMSE in the medical record is also needed; in most records, there was no indication of the MMSE being given, and in most cases, it was impossible to determine if the MMSE was not attempted, or if it was conducted and simply not recorded. As a result, it is impossible to determine what the cognitive status was for patients without a score if the patients did not receive the MOCA later. The method of reconstructing MMSE scores may be inappropriate; the method has not been validated and it was done by only one reviewer. It is impossible to be certain that the sections that were recorded in the medical record were the entirety of the exam attempted. As a result, patients may have taken the entire exam but were only recorded as being given a partial exam; their scores may not be truly accurate. However, these data represent clinical practice, demonstrating the difficulty in providing consistent cognitive assessments to this patient cohort.

This study was done using data collected at one site, UPMC Presbyterian and Montefiore hospitals. While a single site may not be representative of the entire population of cardiac arrest survivors, it provides an assessment of these patients in a tri-state region with a population of approximately 3 million people.<sup>58</sup>

#### **4.4 Public Health Significance**

As previously mentioned, cardiac arrest is a significant public health issue in the United States. Over 500,000 people suffer from one each year,<sup>1</sup> and approximately 9% will survive with “good” neurological outcomes.<sup>16</sup> This equates to 45,000 survivors each year in the United States alone being discharged from the hospital with neurological status similar to the status of the participants of this study. This study was restricted to the best of the best for functional performance, and even still, the majority of participants exhibited cognitive impairment, which in some cases was severe. This study identified key factors that can influence cognitive performance prior to discharge from the hospital, which could be important considerations as patients continue to recover at home.

While etiology was not predictive of cognitive status as determined by the MOCA when certain time elements were considered in the in-hospital setting, in-hospital cognitive assessments remain valuable tools for clinicians as they prepare patients for discharge. The MOCA is a quick and easy tool to determine if patients are suffering from abnormal cognition after cardiac arrest. As the mean MOCA score in this study was below the threshold for normal cognition, it appears that impaired cognition is a widespread problem among this specific patient population, despite its relatively increased survival rates compared to the literature. This study identified that most cardiac arrest survivors, regardless of etiology, had significant issues with delayed recall. Survivors of respiratory arrests in particular had significant issues with attention and language compared to the other etiologies. These domains may be targeted for specific cognitive rehabilitation in this patient population.

This study supports the use of the MOCA serially to assess the impact of timing on cognitive performance after cardiac arrest. Early determination of the presence and type of

cognitive impairment allows for early intervention and support, and cognitive recovery following cardiac arrest can be monitored and tracked after patients leave the hospital. It is still necessary to understand in finer detail what the relationship is between timing and cognitive performance, and how time spent in the ICU may impact cognition. Knowledge that timing of exam can impact score more than etiology and that scores improve over time will improve the focus of healthcare and rehabilitation for survivors prior to hospital discharge and in the months of recovery afterward.

## **5.0 Conclusions**

Cardiac arrest etiology did not predict the MOCA score. However, respiratory, traumatic, and other/unknown etiology arrests were several times more likely to exhibit abnormal cognition than cardiac etiology arrest survivors. Delayed recall was severely affected in all etiology categories, and attention and language were the domains most significantly impacted after respiratory cardiac arrest. The etiological findings were nullified when time from arrest to cognitive examination and total length of hospital stay were controlled for. It appears that the latter factors are more influential on cognitive performance than cardiac arrest etiology. Future work will identify why the time to exam administration is so crucial to cognitive exam performance.

## Appendix Table and Figures

**Table 1. Cognitive Exams in Various Populations**

<b>Title, Authors, Journal, Year Published</b>	<b>Cognitive Examination</b>	<b>Time of assessment</b>	<b>Disease Population</b>	<b>Study N</b>
“The Montreal Cognitive Assessment: Short Cognitive Evaluation in a Large Stroke Trial” Cumming et al. <sup>55</sup> <i>Stroke</i> , 2011	Montreal Cognitive Assessment	3 months after stroke	AVERT trial survivors (stroke)	294
“Mild Cognitive Impairment and Dementia Prevalence: the Atherosclerosis Risk in Communities Neurocognitive Study” Knopman et al. <sup>59</sup> <i>Alzheimer’s &amp; Dementia</i> , 2016	Wechsler Memory Scale-III	Baseline (telephone interview)	Surviving ARIC participants (community members), USA	6471
“Serum Cholesterol and Cognitive Performance in the Framingham Heart Study” Elias et al. <sup>60</sup> <i>Psychosomatic Medicine</i> , 2005	Wechsler Adult Intelligence Scale, Wechsler Memory Scale, Multilingual Aphasia Examination	14 <sup>th</sup> or 15 <sup>th</sup> biennial examination	Surviving Framingham Heart Study participants (community members), Massachusetts, USA	789 men, 1105 women
“Cognitive and Neuropsychiatric Correlates of Functional Impairment Across the Continuum of No Cognitive Impairment to Dementia” Burton et al. <sup>61</sup> <i>Arch Clin Neuropsychol</i> , 2018	Mini-Mental State Exam	Baseline (clinic recruitment)	Rural and Remote Memory Clinic patients, Saskatchewan, Canada	N=403 No CI=75 Mild CI=75 Alzheimer’s Disease Dementia = 139 Non-AD Dementia=114
“The Montreal Cognitive Assessment: Normative Data from a Large Swedish Population-Based Cohort” Borland et al. <sup>57</sup> <i>J Alzheimers Dis</i> , 2017	Montreal Cognitive Assessment	Baseline (in-person clinic interview)	Randomly selected elderly cohort from EPIC study, excluding cognitively impaired participants	758
“The Utility of the Cognitive Function Instrument (CFI) to Detect Cognitive Decline in Non-Demented Older Adults” Li et al. <sup>62</sup> <i>J Alzheimers Dis.</i> , 2019	Modified Mini-Mental State Exam, Free and Cued Selective Reminding Test	Baseline (in-person clinic interview)	Non-demented Alzheimer’s Disease Cooperative Study participants and their partners	644

**Table 1 Continued**

“Association between Dietary Sodium Intake and Cognitive Function in Older Adults” Rush et al. <sup>63</sup> J Nutr Health Aging, 2017	Trails Making Test part B, Mini-Mental State Exam, Verbal Fluency Test	1992-1994 clinic visit	Southern California community members of the Rancho Bernardo longitudinal study	373 white men, 552 white women aged 50-96
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**Table 2. Reconstructed MMSE Scores from Medical Record Review**

Text from Medical Record	Scored Points	Possible Points	Percentile Score	Low-bar MMSE
“Awake, alert, oriented to person place time, month year, day of week, and number day of month. Recall 0/3 delayed, 2/5 for WORLD, follows commands, identifies objects”	20	26	76.9%	Pass
“A and O MMSE improved Orientation 8/10, though she was at Mercy, Spells WORLD =WOURLD but was able to spell DLOUW. 1/3 5 min recall.”	13	18	72.2%	Pass
“1/3 delayed recall, 1/5 for serial 7’s, AAO*4”	12	18	66.7%	Pass
“A+Ox3. 3/3 registration, 0/3 recall. Perfect serial 7s.”	15	21	71.4%	Pass
“1/5 attention, 0 of 3 delayed recall, 8 of 10 orientation.”	9	18	50.0%	Fail
“On MMSE, could not complete all tasks but orientation 6/10, delayed memory 2/3, unable to do WORLD”	8	18	44.4%	Fail

**Table 3. All PCAS Patients by Cardiac Arrest Etiology with Demographics**

Etiology	PCAS patients, n (%)	Male n (%)	Male Coefficient (p-value)	Age, years Mean (SE)	Age Coefficient (p-value)
<b>All</b>	1999 (100)	1,160 (100)	(58.0) ---	59.3 (0.4)	---
<b>Cardiac</b>	662 (33.1)	386 (58.3)	<i>Ref</i>	61.3 (0.6)	<i>Ref</i>
<b>Respiratory</b>	556 (27.8)	315 (56.7)	-0.02 (p=0.561)	<b>53.7 (0.8)</b>	<b>-7.65 (p=0.000)*</b>
<b>Trauma</b>	96 (4.8)	52 (54.2)	-0.04 (p=0.443)	61.1 (1.7)	-0.26 (p=0.884)
<b>Other/Unknown</b>	685 (34.3)	407 (59.4)	0.01 (p=0.681)	61.7 (0.6)	0.36 (p=0.688)

\*Statistical significance

**Table 4. MOCA Participants by Cardiac Arrest Etiology with Demographics**

Etiology	MOCA participants, n (%)	% Male	Male Coefficient (p-value)	Mean (SD) Age, years	Age Coefficient (p-value)
All	192 (100.0)	59.2	---	56.2 (17.3)	---
Cardiac	104 (54.2)	59.6	<i>Ref</i>	58.2 (17.1)	<i>Ref</i>
Respiratory	35 (18.2)	41.4	-0.17 (p=0.086)	57.6 (13.0)	-0.2 (p=0.956)
Trauma	4 (2.1)	40.0	-0.10 (p=0.705)	43.8 (9.0)	-10.1 (p=0.221)
Other/Unknown	49 (18.3)	63.2	-0.00 (p=0.960)	55.8 (20.7)	-3.1 (p=0.270)

**Table 5. Cardiac Arrest Etiology by Modified Rankin Scale**

Etiology	mRS 0, n(%)	mRS 1, n(%)	mRS 2, n(%)	mRS 3, n(%)	mRS 4, n(%)	mRS 5, n(%)	mRS 6, n(%)	Unknown, n(%)
All Cause N=1,999	25 (1.21)	81 (4.05)	110 (5.50)	88 (4.40)	250 (12.51)	190 (9.50)	1,246 (62.33)	9 (0.45)
Cardiac n=662	11 (1.66)	42 (6.34)	62 (9.37)	43 (6.50)	124 (18.73)	59 (8.91)	318 (48.04)	3 (0.45)
Respiratory n=556	6 (1.08)	17 (3.06)	13 (2.34)	17 (3.06)	58 (10.43)	64 (11.51)	381 (68.53)	0 (0.00)
Trauma n=96	0 (0.00)	1 (1.04)	5 (5.21)	1 (1.04)	6 (6.25)	8 (8.33)	75 (78.13)	0 (0.00)
Other/Unknown n=685	8 (1.17)	21 (3.07)	30 (4.38)	27 (3.94)	62 (9.05)	59 (8.61)	472 (68.91)	6 (0.88)
	No Symptoms		Slight Disability		Severe Disability		Dead	



**Table 6. Etiology by MOCA Status for Functional mRS Patients**

<b>Etiology</b>	<b>Received MOCA</b>	<b>Did Not Receive MOCA</b>
Cardiac, %	54.2	47.7
Respiratory, %	18.2	21.4
Trauma, %	2.1	2.6
Other/Unknown, %	25.5	28.4
Non-Cardiac, %	45.8	52.4

**Table 7. Length-of-Stay Analyses**

	<b>Hospital Length of Stay, median (IQR) days</b>						<b>ICU Length of Stay, median (IQR) days</b>					
	<b>MMSE</b>			<b>MOCA</b>			<b>MMSE</b>			<b>MOCA</b>		
	<b>Yes</b>	<b>No</b>	<b>p-value</b>	<b>Yes</b>	<b>No</b>	<b>p-value</b>	<b>Yes</b>	<b>No</b>	<b>p-value</b>	<b>Yes</b>	<b>No</b>	<b>p-value</b>
<b>All Patients</b>	11 (7-18)	4 (1-11)	0.0001	10 (7-16)	4 (1-12)	0.0001	5 (2-9)	3 (1-7)	0.0001	4 (2-7)	3 (1-7)	0.0079
<b>All Etiology Survivors Only</b>	11 (7-18)	15 (8-25)	0.0002	10 (7-16)	15 (7-25)	0.0001	5 (2-9)	7 (3-15)	0.0001	4 (2-7)	7 (3-15)	0.0001
<b>All Non-Traumatic Patients</b>	11 (7-19)	4 (1-11)	0.0001	10 (7-18)	4 (1-11)	0.0001	5 (2-8)	3 (1-7)	0.0001	4 (2-7)	3 (1-7)	0.0068
<b>All Non-Traumatic Survivors</b>	11 (7-18)	15 (7-25)	0.0003	10 (7-17)	15 (7-24)	0.0001	5 (2-9)	7 (3-15)	0.0001	4 (2-7)	7 (3-15)	0.0001

**Table 8. Educational Attainment in MOCA Group**

Education Level	n (%)	Mean (SE) MOCA Score	Coefficient	p-value
Less than 12 years/did not finish high school†	4 (2.1)	68.3 (2.2)	-2.9	0.715
Some high school‡	3 (1.6)	52.2 (15.7)	-19.0	<b>0.036*</b>
Graduated from high school	38 (19.8)	71.8 (2.4)	0.6	0.846
Completed GED	5 (2.6)	67.3 (3.2)	-3.9	0.583
Post-high school/technical school	52 (27.1)	76.4 (2.0)	5.2	0.060
College	8 (4.2)	81.4 (4.0)	10.2	0.073
Post-college	1 (0.5)	60 (--)	-11.2	0.467
Master's degree or higher	3 (1.6)	86.7 (3.3)	15.5	0.086
Not documented	78 (40.6)	71.2 (1.8)	<i>Ref</i>	---

\*Statistical significance

**Table 9. Mean MOCA Percent Score by Etiology**

Etiology	Mean (SE) MOCA Score	Median (IQR) MOCA Score	Coeff.	p-value
Cardiac	74.7 (1.5)	76.7 (18.7)	<i>Ref</i>	---
Respiratory	69.3 (2.4)	70.0 (20.0)	-5.5	0.073
Trauma	70.1 (6.4)	68.3 (19.8)	-4.6	0.561
Other/Unknown	71.4 (2.4)	73.3 (21.8)	-3.3	0.214

**Table 10. Odds of Abnormal Cognition by Etiology – Binomial Regression**

<b>Etiology</b>	<b>Odds Ratio</b>	<b>95% CI</b>	<b>p-value</b>
<b>Respiratory</b>	2.52	1.65-3.87	<b>0.000*</b>
<b>Trauma</b>	3.43	1.23-9.59	<b>0.018*</b>
<b>Other/Unknown</b>	2.18	1.49-3.18	<b>0.000*</b>

- Statistical model contained cognition status and etiology
- Cardiac etiology was the reference category
- \*Statistical significance

**Table 11. MOCA Subscales by Etiology – Binomial Regression**

	<b>Cardiac Mean (SE) Score; Reference</b>	<b>Respiratory Mean (SE) Score; Coeff, p-value</b>	<b>Trauma Mean (SE) Score; Coeff, p-value</b>	<b>Other/Unknown Mean (SE) Score; Coeff, p-value</b>
<b>Visuospatial/Exec.</b> range 0-5	3.5 (0.13) ---	3.09 (0.23) -0.42, 0.129	2.75 (1.10) -0.75, 0.281	3.29 (0.22) -0.21, 0.406
<b>Naming</b> range 0-3	2.77 (0.05) ---	2.71 (0.10) -0.05, 0.588	2.25 (0.25) -0.52, 0.051	2.79 (0.06) 0.08, 0.349
<b>Attention</b> range 0-6	4.90 (0.13) ---	<b>4.11 (0.25)</b> <b>-0.79, 0.004*</b>	5.5 (0.29) 0.59, 0.395	4.79 (0.21) -0.20, 0.412
<b>Language</b> range 0-3	2.27 (0.09) ---	<b>1.89 (0.17)</b> <b>-0.38, 0.040*</b>	2.25 (0.25) -0.02, 0.968	2.13 (0.13) -0.05, 0.735
<b>Abstraction</b> range 0-3	1.93 (0.02) ---	1.89 (0.07) -0.05, 0.452	1.75 (0.25) -0.18, 0.263	1.91 (0.04) 0.02, 0.688
<b>Delayed Recall</b> range 0-5	1.67 (0.15) ---	1.83 (0.28) -0.15, 0.602	1.50 (0.29) -0.17, 0.830	1.89 (0.25) 0.20, 0.469
<b>Orientation</b> range 0-6	5.34 (0.09) ---	5.06 (0.21) -0.28, 0.184	4.75 (0.48) -0.59, 0.286	5.28 (0.16) -0.19, 0.330

- Models contained MOCA subscale and etiology category
- \*Statistical significance

**Table 12. Odds of Abnormal Cognition by Etiology – Multivariate Model 1**

<b>Etiology</b>	<b>Odds Ratio</b>	<b>95% CI</b>	<b>p-value</b>
<b>Respiratory</b>	2.06	1.27-3.35	<b>0.003*</b>
<b>Trauma</b>	1.76	0.61-5.12	0.296
<b>Other/Unknown</b>	1.81	1.17-2.78	<b>0.007*</b>

- Model contained cognition status and etiology category while controlling for age, sex, witnessed status, coma status, ICU length of stay
- Cardiac etiology was the reference category
- \*Statistical significance

**Table 13. Odds of Abnormal Cognition by Etiology – Multivariate Model 2**

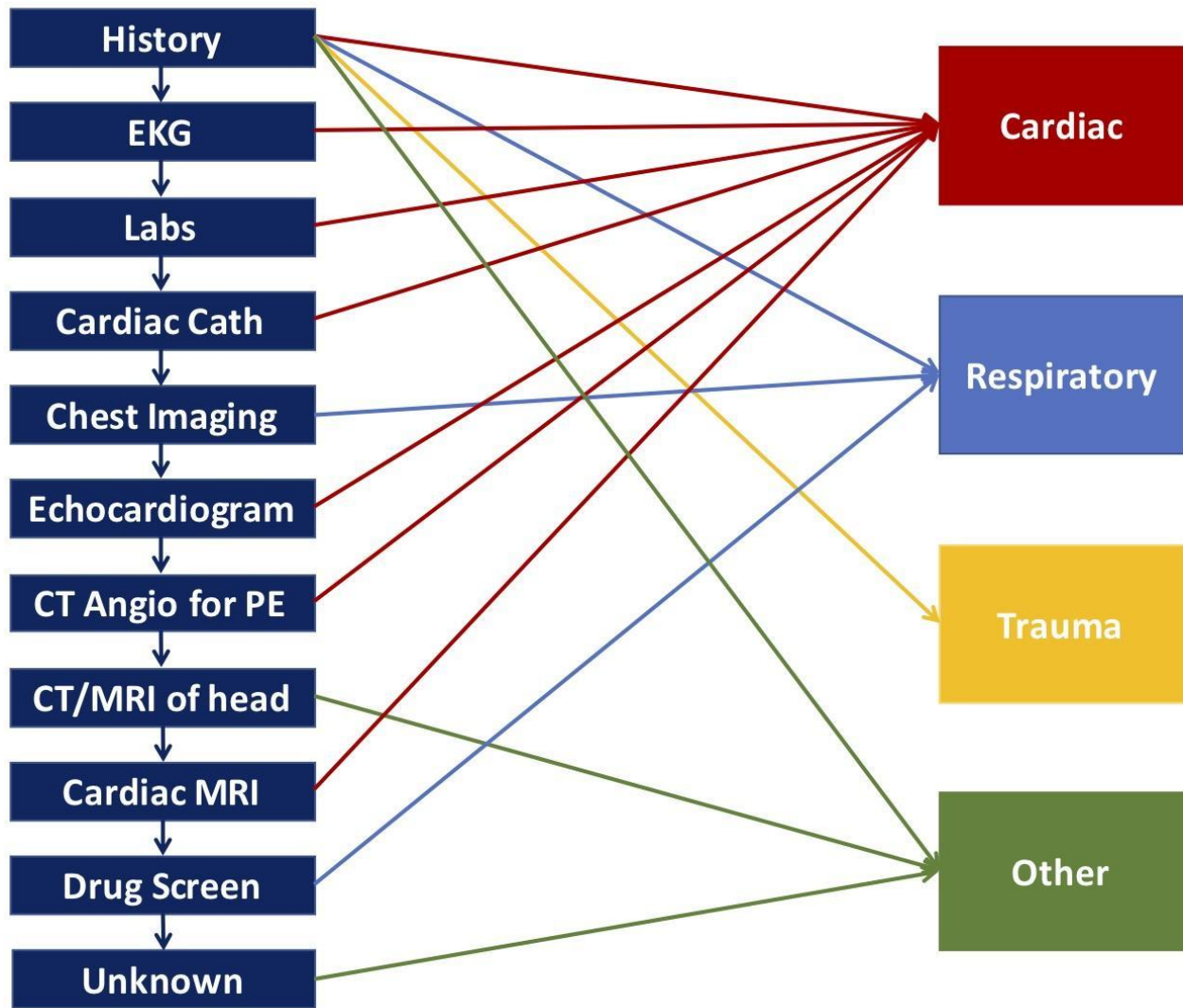
<b>Etiology</b>	<b>Odds Ratio</b>	<b>95% CI</b>	<b>p-value</b>
<b>Respiratory</b>	0.73	0.21-2.46	0.606
<b>Trauma</b>	---	---	---
<b>Other/Unknown</b>	0.58	0.19-1.79	0.343

- Model contained cognition status and etiology category while controlling for age, sex, witnessed status, coma status, ICU length of stay, time from arrest to MOCA
- Cardiac etiology was the reference category

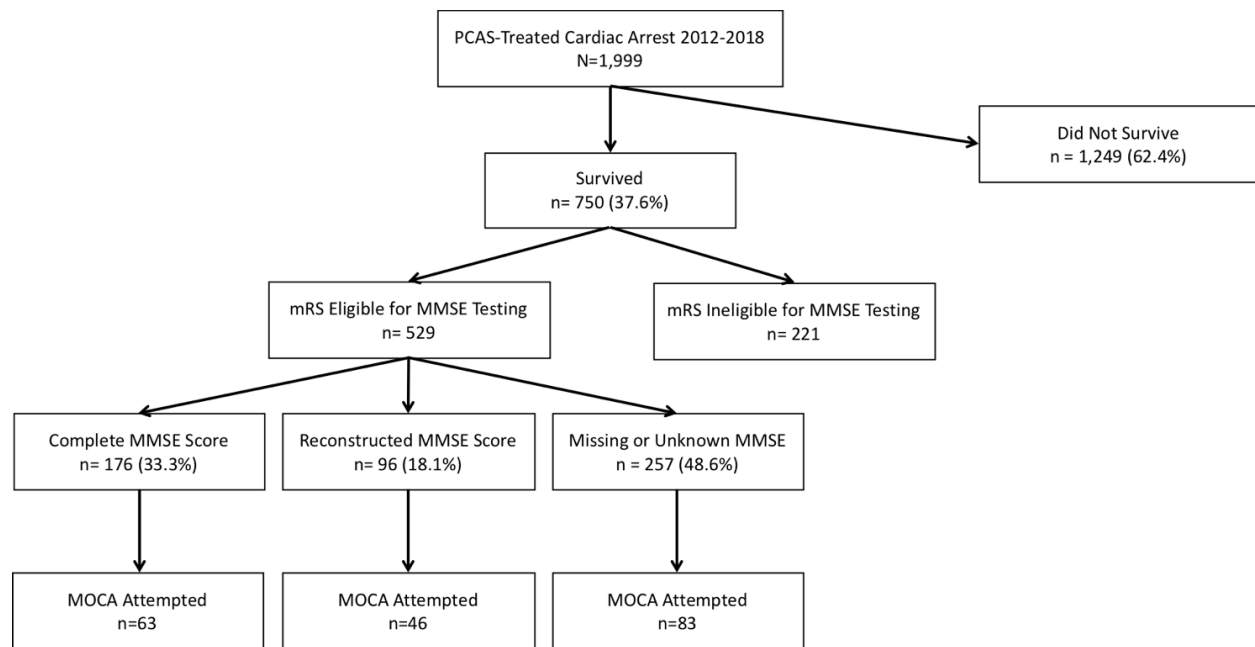
**Table 14. MOCA Subscales by Etiology – Multivariate Model**

	<b>Cardiac Mean (SE) Score; Reference</b>	<b>Respiratory Mean (SE) Score; Coeff, p-value</b>	<b>Trauma Mean (SE) Score; Coeff, p-value</b>	<b>Other/Unknown Mean (SE) Score; Coeff, p-value</b>
<b>Visuospatial/Exec.</b> range 0-5	3.5 (0.13) ---	3.09 (0.23) -0.23, 0.398	2.75 (1.10) -1.01, 0.136	3.29 (0.22) -0.22, 0.408
<b>Naming</b> range 0-3	2.77 (0.05) ---	2.71 (0.10) -0.02, 0.810	2.25 (0.25) -0.48, 0.058	2.79 (0.06) 0.05, 0.588
<b>Attention</b> range 0-6	4.90 (0.13) ---	<b>4.11 (0.25)</b> <b>-0.57, 0.048*</b>	5.5 (0.29) 0.42, 0.551	4.79 (0.21) -0.14, 0.602
<b>Language</b> range 0-3	2.27 (0.09) ---	1.89 (0.17) -0.25, 0.176	2.25 (0.25) -0.17, 0.707	2.13 (0.13) -0.12, 0.492
<b>Abstraction</b> range 0-3	1.93 (0.02) ---	1.89 (0.07) -0.05, 0.451	1.75 (0.25) -0.20, 0.217	1.91 (0.04) 0.00, 0.972
<b>Delayed Recall</b> range 0-5	1.67 (0.15) ---	1.83 (0.28) -0.31, 0.338	1.50 (0.29) -0.24, 0.760	1.89 (0.25) 0.03, 0.916
<b>Orientation</b> range 0-6	5.34 (0.09) ---	5.06 (0.21) -0.28, 0.188	4.75 (0.48) -0.75, 0.158	5.28 (0.16) -0.17, 0.393

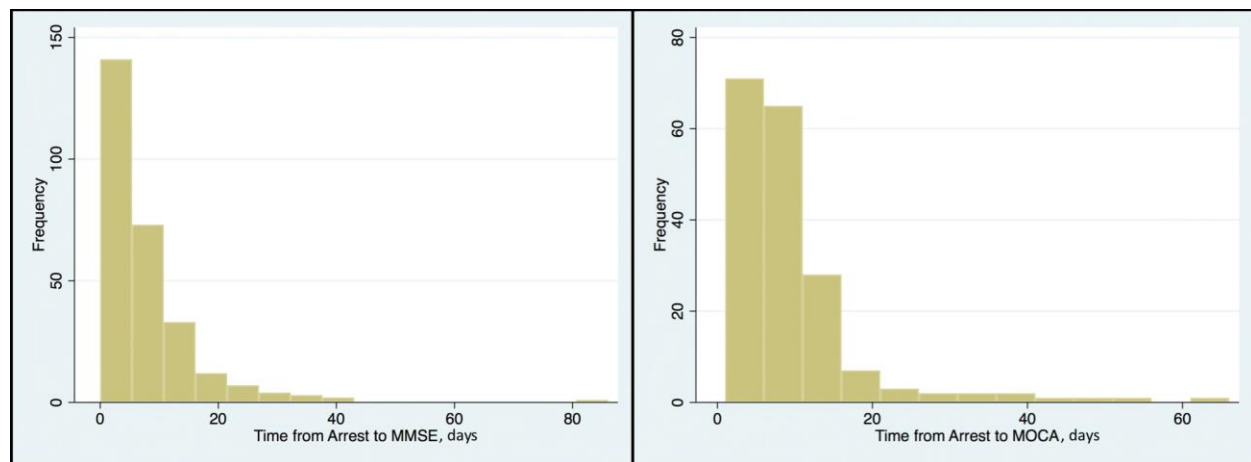
- Models contained MOCA subscale and etiology category while controlling for age, sex, witnessed status, coma status, ICU length of stay
- \*Statistical significance



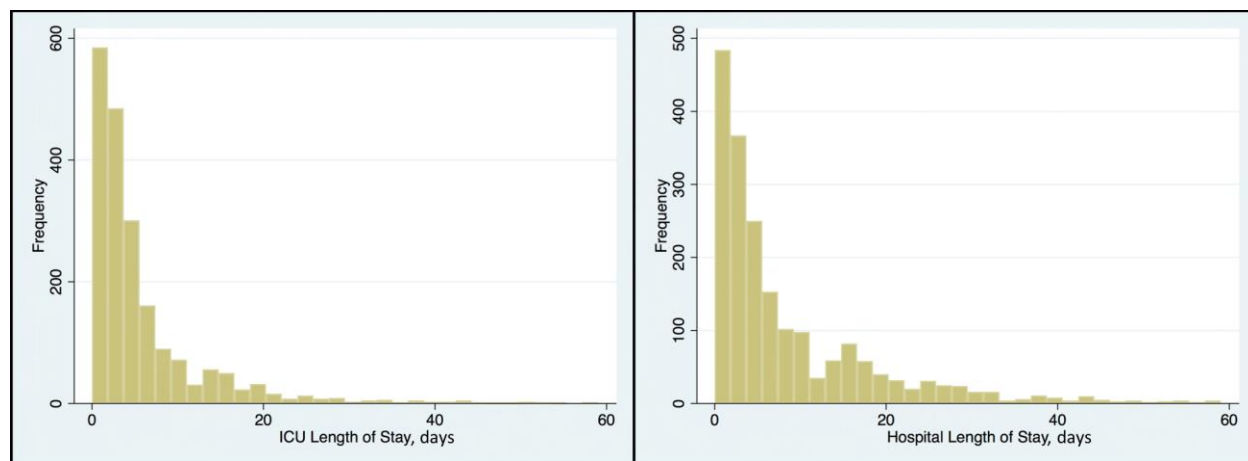
**Figure 1. Flowchart for Cardiac Arrest Etiology Grouping**



**Figure 2. Patient Enrollment Flow Diagram**

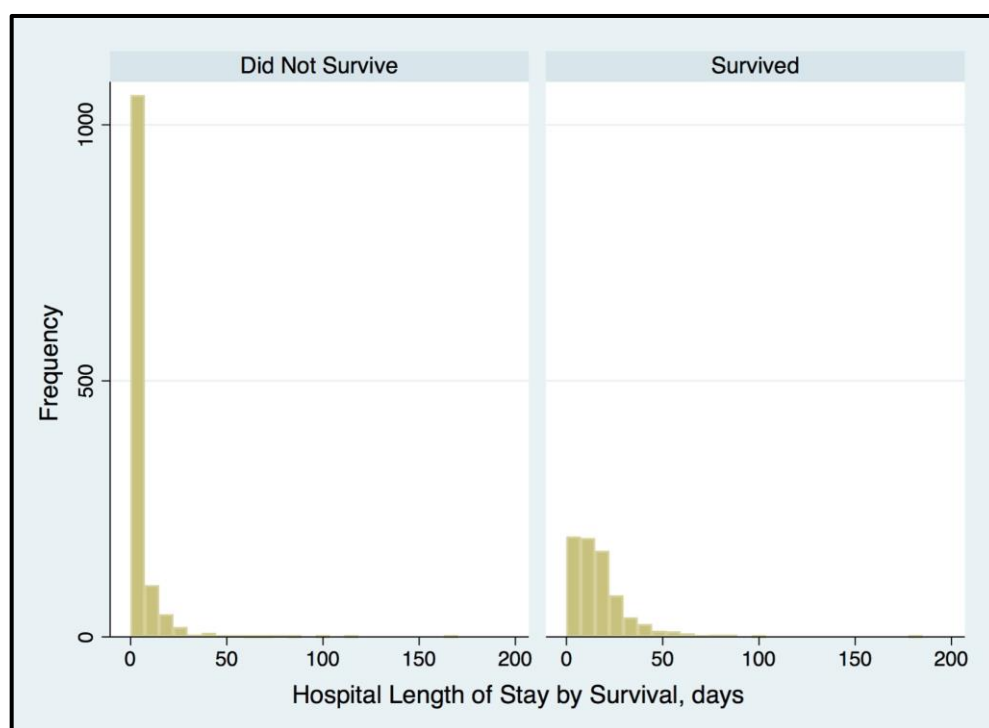


**Figure 3. Time Interval Histograms**



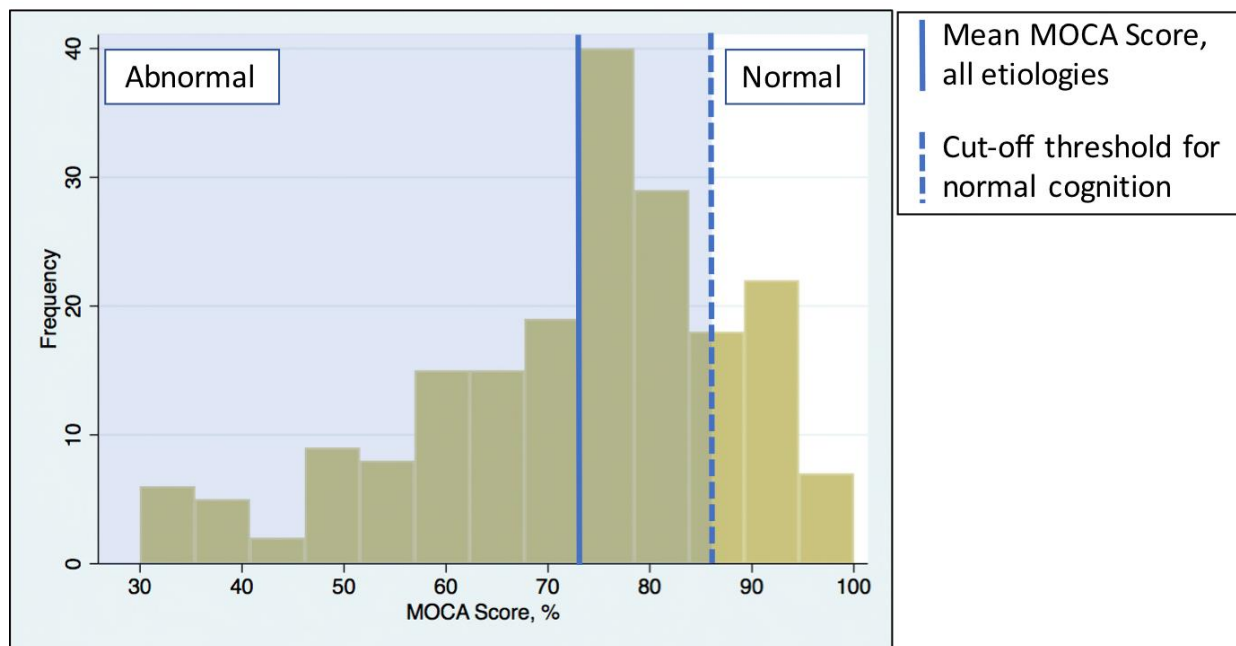
Truncated to 60 days; max ICU LOS: 167 days, max hospital LOS: 185 days

**Figure 4. Length-of-Stay Histograms**

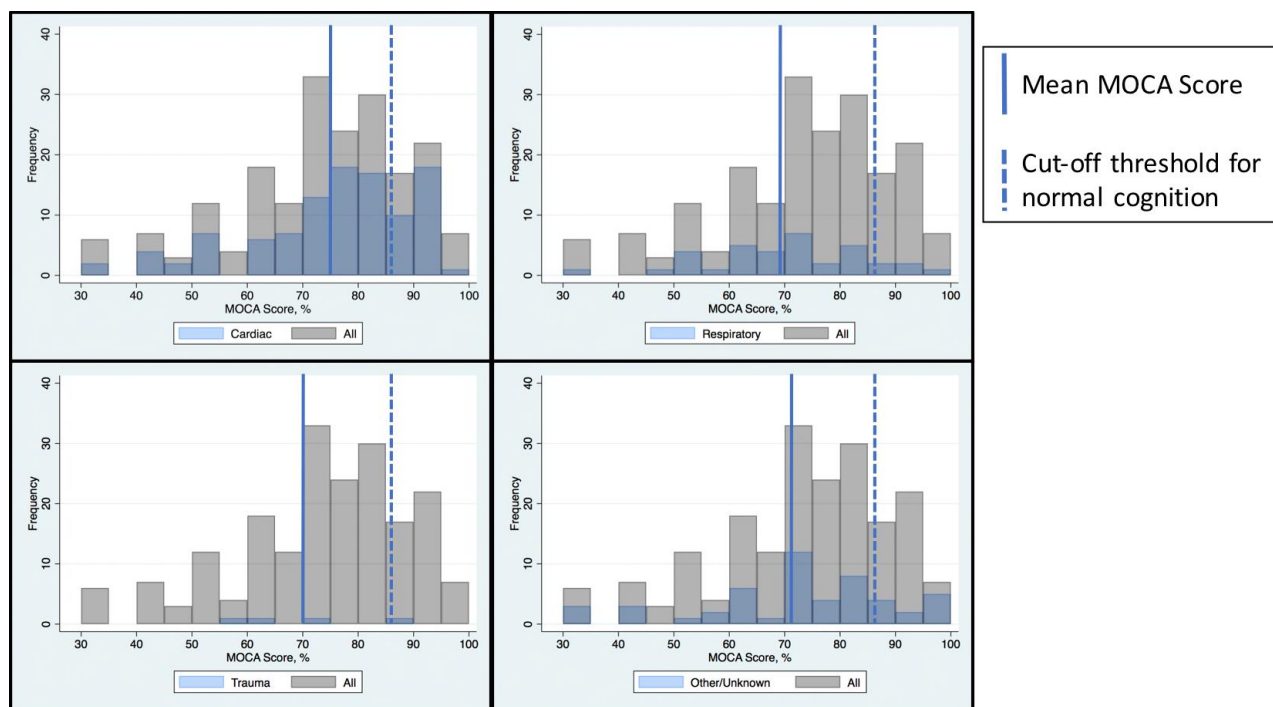


**Figure 5. Hospital Length-of-Stay by Survival Status**

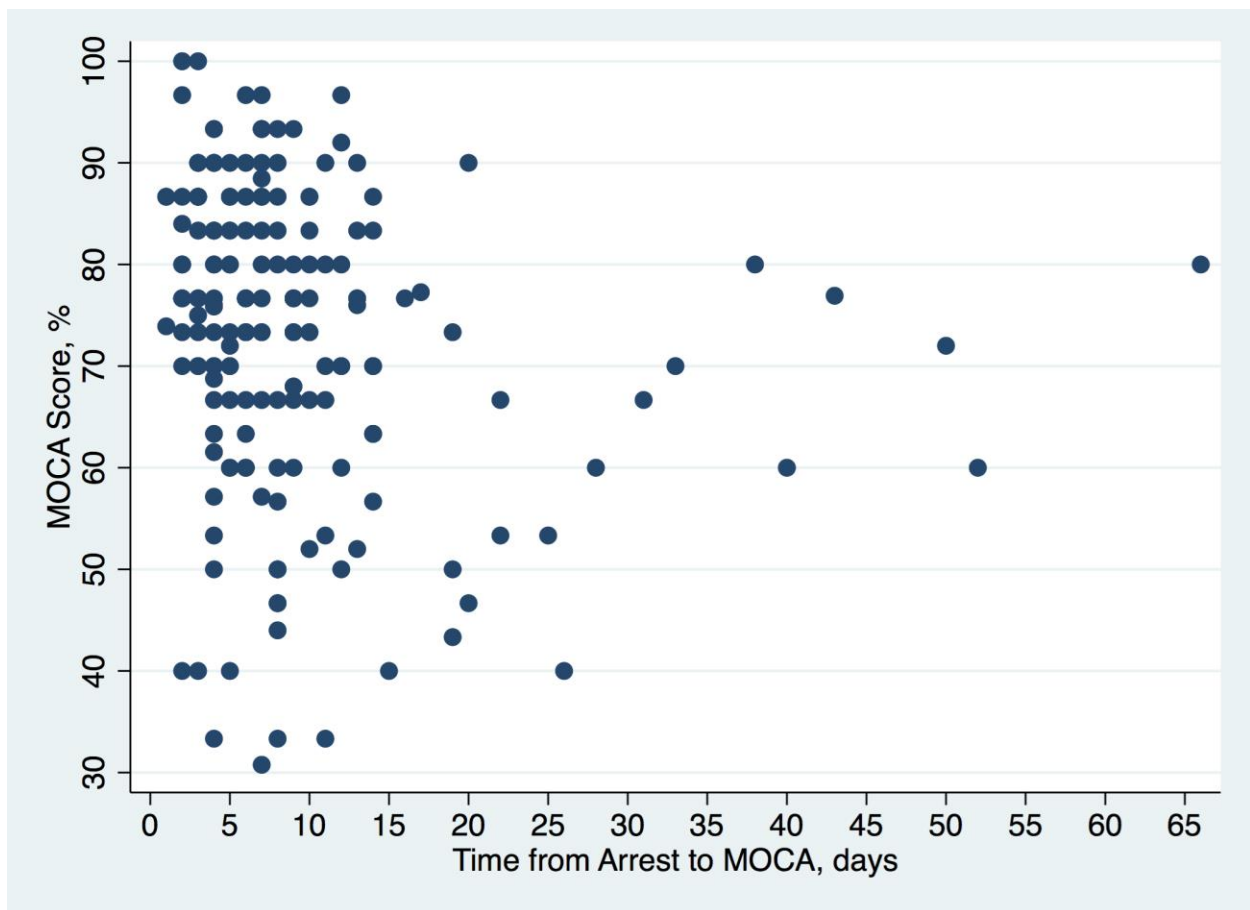




**Figure 6. Overall MOCA Score Distribution**



**Figure 7. MOCA Score Distribution by Etiology**



**Figure 8. Time from Cardiac Arrest to MOCA Administration vs. MOCA Percent Score**

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